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Prediction of blood cyclosporine concentrations in non-obese and obese hematologic patients with multidrug resistance using total, lean and different adipose factor dosing body weights

Sir,

Cyclosporine (CsA) is a highly lipophilic cyclic polypeptide drug,[1] thus better predictions of blood CsA concentrations would be expected from using *total body weight* (TBW) rather than *lean body weight* (LBW) or *adipose factor dosing body weight* (AFDBW). However, several studies show that CsA distribution correlates better with LBW in obese patients and suggest that CsA steady-state concentrations mainly depend on LBW.[2,3] This leads to difficulty in choosing which body weight to use to optimize CsA dosage regimens and predict blood CsA concentrations in non-obese and obese patients.

Thirteen female and twenty-eight male hematologic patients with multidrug resistance were treated by continuous intravenous CsA infusion (Table 1). Blood CsA concentrations were monitored about 4 times a day during infusion and 11 times after infusion (0, 0.5, 1, 2, 3, 5, 7, 9, 12, 24, and 36 hours after infusion), and were immediately analyzed using a fluorescence polarization immunoassay method (TDx, Abbott Laboratories, Diagnostic Division, Irving, TX, USA).[5]

The PKS program (Abbottbase Pharmacokinetic System, version 1.10, Abbott Laboratories, IL, USA, 1992) was used to predict blood CsA concentration using LBW, 25% AFDBW, 50% AFDBW, 75% AFDBW and TBW with a two-compartment model with volume of distribution in the central compartment (V_c=0.70±0.26 L/kg), clearance (CL=0.25±0.08 L/h/kg) and intercompartment rate constants (k_{12}=0.52±0.31 and k_{21}=0.07±0.02/h).[6,7] LBW = –111.621 + (3.636× height in inches) for adult females and LBW = –130.736 + (4.064×height in inches) for adult males. Dosing body weight = LBW + adipose factor × (TBW – LBW)/100, where adipose factor is set at 25%, 50% and 75%, respectively.

The measured and predicted concentrations were used to calculate percentage prediction errors [100× (predicted concentration – measured concentration)/ (measured concentration)][8] and absolute/relative performances.[9]

Blood CsA concentrations were divided into pre-steady-state, steady-state (infusion rate/clearance)[10] and post-steady-state. Table 2 shows the percentage prediction errors. The Friedman ANOVA test indicates that the medians among five dosing body weights at each kinetic state are not equal at $p<0.001$

Table 1. Patients demographics and CsA dosage.

Patients	*Obese situation*	*Numbers*	*Age (years)*	*Height (cm)*	*TBW (kg)*	*LBW (kg)*	*Obesity index (kg/m²)*	*TBW Dose (mg/kg/day)*	*LBW Dose (mg/kg/day)*	*IVT (days)*
Female	non-obese	6	60±6	165±7	64±9	56.6±4.9	23.4±1.2	9.6±2.7	10.8±2.8	3.7±1.0
	moderately obese	7	58±4	160±3	67±5	53.3±2.0	26.1±1.0	9.9±1.2	12.4±1.4	3.6±1.2
Male	non-obese	12	38±15	172±7	70±5	66.7±5.2	23.7±0.7	11.3±1.8	12.0±2.1	3.4±1.2
	moderately obese	14	44±12	172±3	78±5	65.7±2.2	26.5±1.5	10.4±2.3	12.3±2.6	4.2±0.4
	seriously obese	2	51±17	178±11	103±19	69.7±7.7	32.3±2.2	10.5±0.9	15.4±2.4	2.3±2.2

The data are expressed as mean±SD. Non-obese, moderately obese and seriously obese are defined as obesity indices <25 kg/m², 25-29.9 kg/m² and 30-39.9 kg/m², respectively.[4] IVT, the duration of the continuous intravenous infusion. The average time interval between two courses is 77±73 days (mean±SD). Statistical differences were found between TBW and LBW, between TBW and LBW doses at p<0.05 level (the paired Student's t-test). TBW and LBW doses were calculated by dividing the daily dose by TBW and LBW, respectively.

Table 2. Percentage prediction errors.

Gender	Obese situation	kinetic state	n	TBW	75%AFDBW	50%AFDBW	25%AFDBW	LBW
Female	Non-obese	pre-steady state	10	-15.8 (-39.6 – -5.0)	-14.1 (-37.2 – -3.3)	-12.3 (-34.5 – -1.5)	-10.4 (-32.5 – 0.3)	-8.5 (-30.4 – 2.3)
		steady-state	70	19.3 (-20.6 – 37.2)	22.7 (-18.6 – 40.0)	27.0 (-16.5 – 42.3)	32.6 (-14.1 – 44.7)	34.9 (-10.2 – 48.3)
		post-steady state	62	12.9 (-33.7 – 64.9)	15.7 (-32.8 – 66.9)	17.0 (-32.0 – 68.6)	18.3 (-31.1 – 73.6)	21.5 (-30.2-79.6)
	Moderately obese	pre-steady state	15	-22.2 (-28.6 – -13.8)	-17.6 (-24.9 – -9.5)	-12.4 (-20.9 – -4.9)	-6.5 (-16.5 – 0.3)	0.3 (-11.5 – 6.9)
		steady-state	89	22.1 (10.9 – 45.3)	28.8 (15.9 – 52.8)	34.9 (21.89 – 63.1)	42.4 (29.7 – 74.0)	50.8 (38.0 – 86.7)
		post-steady state	65	28.1 (7.3 – 54.9)	33.9 (12.5 – 64.1)	40.3 (18.3 – 74.4)	47.3 (24.5 – 86.2)	55.5 (31.0 – 99.7)
Male	Non-obese	pre-steady state	29	-9.0 (-27.9 – -0.4)	-6.8 (-26.9 – 1.8)	-5.6 (-26.0 – 4.0)	-3.5 (-24.9 – 6.4)	-2.9 (-23.9 – 9.9)
		steady-state	169	27.8 (9.2 – 45.4)	29.6 (10.9 – 48.2)	32.2 (12.5 – 50.9)	34.5 (14.6 – 53.2)	36.4 (16.5 – 55.5)
		post-steady state	122	35.9 (13.1 – 60.3)	38.0 (15.2 – 62.9)	40.0 (17.5 – 65.4)	41.4 (19.2 – 67.4)	43.6 (20.5 – 70.3)
	Moderately obese	pre-steady state	30	-28.2 (-60.4 – -16.4)	-25.2 (-57.9 – -12.2)	-21.9 (-55 – -8.3)	-18.3 (-54.1 – -4.1)	-14.4 (-52.4 – 0.5)
		steady-state	167	-6.5 (-36.2 – 24.8)	-2.8 (-34.1 – 29.1)	1.5 (-29.7 – 33.8)	5.1 (-25.7 – 39.0)	9.8 (-21.3 – 45.9)
		post-steady state	143	6.7 (-38.1 – 53.5)	11.1 (-34.3 – 60.3)	14.7 (-29.9 – 69.8)	22.9 (-25.9 – 78.8)	28.5 (-23.6 – 89.4)
	Seriously obese	pre-steady state	3	-37.7 (-39.5 – -18.6)	-33.2 (-35.0 – -11.3)	-27.8 (-29.8 – 2.7)	-21.5 (-23.6 – 7.8)	-13.9 (-16.2 – 20.9)
		steady-state	14	3.9 (-16.6 – 19.5)	12.8 (-10.4 – 28.5)	23.4 (-3.1 – 38.9)	36.1 (5.4 – 51.1)	49.2 (15.6 – 68.1)
		post-steady state	19	49.9 (16.4 – 74.4)	61.1 (27.7 – 87.5)	76.1 (41.3 – 103.3)	97.2 (58.3 – 127.7)	120.0 (78.2 – 153.8)

Data are presented as the median with interquartile range. n, number of comparisons.

level. The absolute and relative predictive performances show the similar results as percentage prediction errors.

The results suggest using TBW to predict steady-state and post-steady-state blood CsA concentrations and LBW to predict pre-steady-state blood CsA concentrations. The results indirectly support the concept that CsA distribution obeys physicochemical principles.[1]

The estimation of pharmacokinetic parameters using TBW might lead to favorable TBW predictions. The facts that at pre-steady-state CsA might not fully distribute into fatty tissues and CsA concentration might not be dominated by CsA metabolism might lead to favorable LBW predictions.

The time of the continuous intravenous infusion was not identical in each patient, because several patients felt uncomfortable during infusion. Although the ages were not comparable between females and males, we did not consider this problematic because we were mainly concerned with inter-method comparisons at each age group. However, we hope to find patients at different ages in future studies, so we can analyze the integrity of CsA metabolism, which decreases with age, better. We also hope to find seriously obese female patients in future studies.

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Acknowledgments

The PKS program was a kind gift from Abbott Laboratories to Prof. Mario Furlanut.

Key words

Cyclosporine, dosing body weight, hematologic patient with multidrug resistance, inter-method comparison, lean body weight, obesity, prediction, total body weight.

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Indolent lymphoproliferative disease of large granular lymphocytes after lung transplantation

Sir,

Sequential assessment of peripheral blood lymphocyte subsets, useful for following post-transplantation immune reconstitution and detecting infectious or rejection episodes, also allows identification of lymphoproliferative disorders or unusual patterns in some patients.[1] We report the case of a lung transplant recipient who has had, for over 7 years, a persistent immunophenotypic pattern reminiscent of that reported in LGL leukemia and lymphoproliferative diseases of granular lymphocytes (LDGL).

DR, 55 years old, suffered from chronic respiratory insufficiency due to panacinar emphysema with α1-antitrypsin deficiency, which led to a single lung transplant in February 1991. Post-transplant induction immunosuppression was achieved by anti-lymphocyte globulins (ALG; Thymoglobulin, Merieux, Lyon, France), followed by a maintenance regimen of cyclosporine, azathioprine and corticosteroids.

Three episodes of grade I acute rejection were treated by reinforced corticosteroids. Two episodes of bronchiolitis obliterans were controlled by reinforced immunosuppression including ALG treatment in the second instance. Pulmonary function tests have remained stable since.

Herpetic bronchitis was treated by acyclovir. CMV seroconversion, observed concomitantly to the detection of CMV cellular inclusions in a transbronchial biopsy, was treated by ganciclovir. Later, a CMV and *Pneumocystis carinii* lung infection developed which prompted treatment with ganciclovir and sulfamethoxazole-trimethoprim. Antibiotic therapy was necessary to clear several infectious episodes due to *Haemophilus influenzae*, *Aspergillus fumigatus* and *Pseudomonas aeruginosa*. Two epidermoid carcinomas developed in 1996 and in 1998; they were resolved after surgery and chemotherapy.

Sequential immunophenotyping of PBL subsets was performed in the same Immunology laboratory at regular intervals over 7 years (Figure 1) by flow cytometry (Coulter Corporation, Hialeah, FL, USA; reagents from Coulter Corporation and Immunotech, Marseille, France). Post-transplantation and during immunosuppressive treatment, there was a progressive restoration of the different subsets which had collapsed after ALG treatment. From September 1992 on, however, the level of T-cell subsets decreased severely to around 10%, i.e. absolute numbers of $0.11\pm0.05\times10^9$/L, associated with persistently high levels of CD57$^+$ cells (mean overall level out of ALG treatment 60.5±19%, $0.86\pm0.39\times10^9$/L). White blood cell and lymphocyte counts remained within normal ranges, there being steady levels of around 4×10^9/L polymorphonuclear cells. Cytologic examination consistently showed over 60% of typical large granular lymphocytes.

Extensive immunophenotypic studies demonstrated that the predominant population of CD57$^+$ lymphocytes expressed surface CD7, CD2 and cytoplasmic CD3, but lacked CD5, CD3, CD4, CD8 and the T-cell receptor. CD16 and CD94 were always present but CD56 expression was only observed occasional-

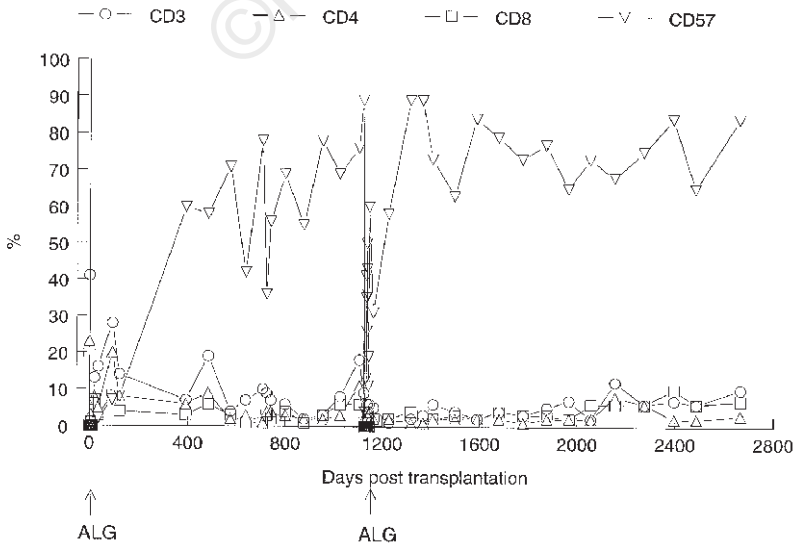

Figure 1. Follow-up of CD3$^+$, CD4$^+$, CD8$^+$ and CD57$^+$ peripheral blood lymphocyte subsets over 7 years following lung transplantation.
ALG: anti-lymphocyte globulin treatments.